Initial Experience with Single-Agent Docetaxel as Neoadjuvant Therapy in Men with Locally Advanced Prostate Cancer

Eric A. Klein, MD,* Robert Dreicer, MD, FACP†

*Glickman Urological Institute, †Taussig Cancer Center, Cleveland Clinic Foundation, Cleveland, OH

Patients with locally advanced prostate cancer have worse outcomes after radical prostatectomy (RP) than patients with more favorable parameters. The findings of large, contemporary, RP series have led investigators at a number of centers to evaluate the potential role of neoadjuvant chemotherapy in patients with locally advanced disease. A currently ongoing study of 28 patients explores the antitumor response of a regimen of single-agent, docetaxel, 40 mg/m^2, administered intravenously on a weekly schedule for 6 weeks to patients with locally advanced prostate cancer before RP. Docetaxel has demonstrated significant antitumor activity in patients with advanced, androgen-independent disease. Study results showed that 75% of patients had reductions in prostate-specific antigen (PSA) levels ranging from 9%–79% at the completion of docetaxel therapy. In 25% of the patients, PSA levels increased by 2%–18% from baseline to completion of chemotherapy. In addition, noncastrate levels of testosterone were maintained in all patients. The docetaxel therapy has also been relatively well tolerated. Reporting of the primary endpoint of pathologic response is pending completion of accrual and surgery.

[Rev Urol. *2003;5(suppl 2):S22-S27*]

Key words: Locally advanced prostate cancer • Radical prostatectomy • Neoadjuvant chemotherapy • Docetaxel

Patients with locally advanced prostate cancer—defined by preoperative characteristics of biopsy Gleason sum, clinical T stage, and serum prostate-specific antigen (PSA) levels—have worse outcomes after radical prostatectomy (RP) than those with more favorable parameters.[1-3] In a recent review of the Cleveland Clinic's experience with radical prostatectomy as monotherapy for

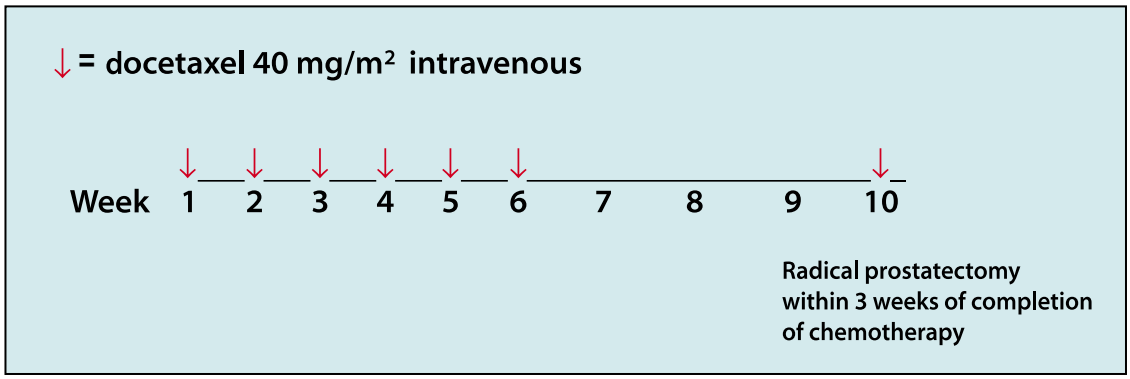

Figure 1. *Treatment schema for phase II clinical trial of neoadjuvant docetaxel before radical prostatectomy in men with locally advanced prostate cancer.*

localized disease, patients with unfavorable pretreatment characteristics (PSA > 10 ng/mL; biopsy Gleason score ≥ 7; or clinical stages T2b, T2c, or T3) had an 8-year, biochemical relapse-free survival rate (bRFS) of 64% compared to 87% for those with favorable parameters.[4] These results are similar to those reported by other groups.[2,3]

Given the potential for both local and systemic problems from this disease subset, various neoadjuvant approaches have been evaluated in an attempt to improve patient outcomes. Because hormonal therapy has a prominent role in prostate cancer management, numerous investigators have evaluated the use of neoadjuvant hormonal therapy. Although early experiences were promising, larger trials of 3 months of neoadjuvant hormonal therapy have failed to demonstrate an improvement in time-to-biochemical-progression following prostatectomy.[5-7] More recently, combinations of hormonal therapy and chemotherapy, administered before both radical prostatectomy and radiotherapy, have been evaluated by several groups with demonstrated feasibility.[8,9] Various groups of investigators are now exploring the utility of chemotherapy in a neoadjuvant setting without hormonal therapy in order to elucidate the antitumor activity of chemotherapy without the confounding influence of hormonal therapy on both normal and abnormal prostate epithelium.[11] The current study, conducted at the Cleveland Clinic Foundation, Dana-Farber Cancer Institute, and Memorial Sloan-Kettering Cancer Center, investigates docetaxel (Taxotere®, Aventis Pharmaceuticals, Bridgewater, NJ) as a single agent in a neoadjuvant setting, based on its tolerability and its demonstrated single-agent activity in advanced prostate cancer.[10]

Study Design

Objectives

This phase II study was designed to determine the activity (PSA response and antitumor activity in the prostate), feasibility, and tolerability of a short, intensive course of docetaxel in patients with locally advanced prostate cancer. Patient follow-up and monitoring was conducted for 24 months after treatment.

Eligibility

Eligible patients were required to meet the following criteria: 1) have histologically documented, locally advanced prostate cancer as defined by serum PSA > 15 ng/mL (with any disease grade or stage), clinical stage T2b, T2c, or T3 (with any PSA or disease grade), or biopsy Gleason score ≥ 8 (with any disease stage or PSA); 2) show no evidence of metastatic disease within 30 days of entry as judged by a physical examination, bone scan, and computed tomography of the abdomen and pelvis; 3) have adequate renal, hepatic, and bone-marrow capacity as defined by serum creatinine < 2.0 mg/dL, bilirubin < 1.5 mg/dL, aspartate transaminase (AST) < 60 mg/dL, absolute neutrophil count ≥ 1500 mm^3, hemoglobin ≥ 9g/dL, and platelet count ≥ 100,000 mm^3; 4) be a candidate for radical prostatectomy based on general medical condition, performance status, and life expectancy; and 5) complete a signed informed consent.

All biopsy specimens were reviewed at our institution, the Cleveland Clinic, for confirmation of the presence of adenocarcinoma and the assignment of a Gleason score. The clinical stage was assigned, based on a digital rectal exam (DRE) by a single surgeon, according to the 1992 American Joint Committee on Cancer (AJCC) criteria.[12] The protocol was approved by our Institutional Review Board and Clinical Trials Scientific Review Committee, and a signed informed consent was obtained from all patients.

The exclusion criteria included prior hormonal therapy (except finasteride for the treatment of obstructive voiding symptoms), chemotherapy, and pelvic radiotherapy, as well as any malignancy other than basal cell carcinoma of the skin within 5 years of entry in the study. The pretreatment evaluation included a complete medical history and physical examina-

tion: complete blood count, serum chemistries, testosterone, PSA, bone scan, and computed tomography of abdomen and pelvis. Testosterone and PSA levels were obtained after chemotherapy and before scheduled radical prostatectomy.

Treatment Plan
Treatment consisted of docetaxel, 40 mg/m^2/wk, administered in 100 cc normal saline intravenously over 30 minutes, weekly × 6 weeks (Figure 1). A dose of 8 mg of dexamethasone was administered orally 12 hours before and immediately before each dose of docetaxel. Before receiving each dose of docetaxel, patients were required to have an absolute neutrophil count of ≥ 1200/mm^3 and a platelet count ≥ 100,000/mm^3. Dose modifications were allowed for grade IV neutropenic fever and any grade 3 or greater nonhematologic toxicity. The Common Toxicity Criteria, version 2.0, were used to report toxicity and adverse events. Radical prostatectomy was performed 2–3 weeks after completion of therapy.

Surgical Therapy
Within 3 weeks after the completion of chemotherapy, all patients underwent bilateral pelvic lymphadenectomy and radical retropubic prostatectomy, according to a standardized technique, under epidural anesthesia. Intermittent compression stockings, applied before the induction of anesthesia, were used for prophylaxis of deep vein thrombosis. Both neurovascular bundles were widely resected in all cases. A cell-salvage device was used for intraoperative autotransfusion. Routine postoperative care was provided as previously reported.[13] The transurethral catheter was removed at 2 weeks after surgery.

Pathological Analysis
All specimens were fixed in formalin for 24–48 hours, inked in two colors (left and right halves), step-sectioned at 3 mm intervals, and evaluated by two pathologists. The histologic analysis included evidence of residual cancer, necrosis, the presence of extracapsular extension, and the status of the surgical margins. Extracapsular extension (ECE) was defined as evidence of prostate cancer in extraprostatic tissue, and positive margins as tumor-touching ink.

Treatment consisted of a dosage of docetaxel at 40 mg/m^2/wk administered in 100 cc normal saline intravenously over 30 minutes, weekly x 6 weeks.

Response Criteria
The study was designed to evaluate the toxicity and response rates to weekly administration of single-agent docetaxel. Although the PSA response to therapy was assessed, the pathologic response was the primary end point. Toxicity was graded using the Common Toxicity Criteria, version 2.0.

Results

Patient Demographics
A total of 28 patients with a median age of 63 years (range, 50–71 years) were enrolled in this trial. The median pretreatment PSA was 8.8 ng/mL (range, 3.9–38.4 ng/mL), and the median Gleason sum was 8 (range, 7–9). Most patients had a clinical stage of T2b or greater. No patients had received prior hormonal therapy. The median interval between completion of chemotherapy and radical prostatectomy was 3.2 weeks (range, 2–5 weeks). Surgical difficulty was slightly to moderately greater for patients who received chemotherapy than for patients who did not receive chemotherapy, and there have been no significant perioperative or postoperative complications. Hospitalizations after surgery averaged 2 days.

Toxicity
The therapy has been relatively well tolerated. Five patients required one week delay in docetaxel treatment to allow recovery from grade 3 neutropenia; no cases of febrile neutropenia occurred. Other toxicities have included grade 3 fatigue (n = 3), grade 2 nail-bed changes (n = 3), and grade 2 edema (n = 2). Most patients experienced grade 1–2 nonpruritic rash.

Responses
The results showed that 21 patients had an improvement in PSA levels at the completion of neoadjuvant docetaxel therapy, with reductions ranging from 9%–79%. In 7 patients, PSA levels increased by 2%–18% from baseline to completion of chemotherapy. Noncastrate levels of testosterone were maintained following chemotherapy in all patients. Reporting of the pathological response is pending the completion of accrual and surgery in all patients.

Discussion

The need for innovative, multimodal approaches to treating locally advanced prostate cancer is illustrated by the results of large, contemporary, radical prostatectomy series.[3,14] Whereas patients with favorable preoperative parameters, organ-confined disease, and negative surgical margins can expect an 8-year, biochemical disease-free survival of 96%,[3] patients with locally advanced disease fare much worse. For example, patients with a Gleason score of

≥ 8 have an actuarial 7- to 10-year biochemical relapse-free survival (bRFS) of only 23%–48%. Similarly, patients with cT2b disease or higher have a bRFS of only 52%–57%.[2,4] These findings have led investigators at a number of centers to evaluate the potential role of neoadjuvant chemotherapy in patients with locally advanced disease.

Klein and coworkers at the Cleveland Clinic Foundation, in a study reported in Clark and colleagues,[8] performed a phase II neoadjuvant trial of estramustine phosphate (Emcyt®, Pharmacia and Upjohn, Kalamazoo, MI) and etoposide (VePesid®, Bristol-Myers Squibb Company, New York) in patients with locally advanced disease (Table 1), using the same entry criteria as the neoadjuvant docetaxel study described above. A total of 18 patients received three preoperative cycles of estramustine 10 mg/kg/d and etoposide 50 mg/m^2/d orally in divided doses on days 1–21 and repeated every 28 days. All 18 patients completed chemotherapy, and 16 underwent radical prostatectomy. Therapy was relatively well tolerated; however, there were 2 episodes of grade 3 neutropenia, 2 patients developed deep venous thrombosis, and 1 patient had a pulmonary embolism.

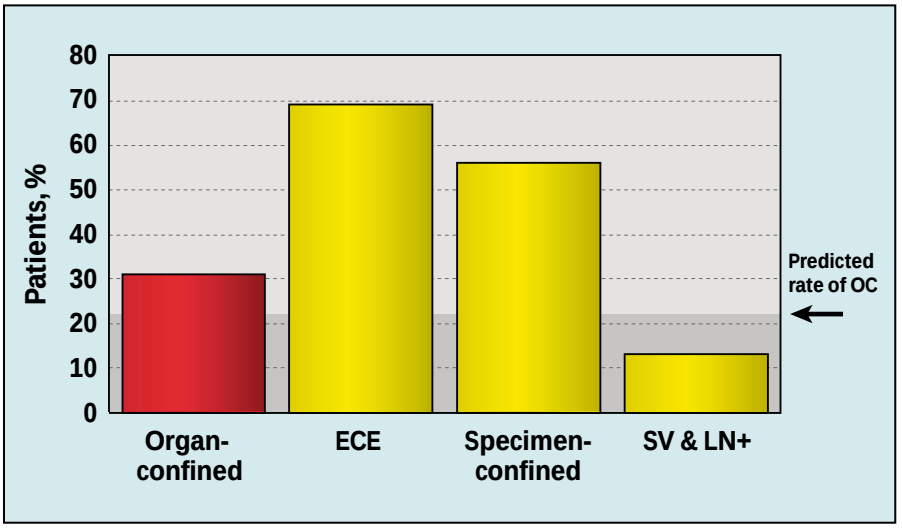

Figure 2. *Pathologic outcomes of a phase II trial of neoadjuvant estramustine phosphate and etoposide before radical prostatectomy. OC, organ-confined (negative margins and no extracapsular extension); ECE, extracapsular extension; specimen-confined, extracapsular extension with negative margins; SV, seminal vesicle invasion; LN+ = lymph-node metastasis. Data from Clark et al.*[8]

The median operative time (time from skin incision to skin closure) was 125 minutes (range, 120–180 minutes), which was slightly longer but not statistically different from the operative time for a contemporaneous group of patients undergoing radical retropubic prostatectomy without neoadjuvant therapy. The final histology demonstrated squamous metaplasia and an androgen-deprivation effect, but no areas of tumor necrosis, and all specimens contained residual carcinoma. The rate of organ-confined disease (31%) was approximately 10% higher than expected, as predicted by the Partin nomograms (Figure 2).[8] There was a relatively high rate of specimen-confined disease (extracapsular extension with negative surgical margins), and only 2 patients (who also had invasion of the seminal vesicle and lymph node metastases) having positive margins, an improvement over recently reported series in which patients with locally advanced prostate cancer disease without neoadjuvant therapy had positive margin rates of 48%–65%.[15,16] All patients in this series achieved undetectable serum PSA levels after surgery.

Recently, a similar trial of neoadjuvant chemohormonal therapy given before radical prostatectomy was reported by Pettaway and associates[17] in a similar cohort of patients. In this trial, preoperative therapy consisted of two 6-week cycles of ketoconazole (Nizoral®, Janssen Pharmaceutica Products, Titusville, NJ) and doxorubicin (Adriamycin®, Pharmacia and Upjohn, Kalamazoo, MI) alternating with vinblastine (Velbe®, Eli Lilly

Table 1
Surgical Outcomes of a Phase II Trial of Neoadjuvant Estramustine Phosphate and Etoposide Before Radical Prostatectomy

Median operative time	125 minutes (range, 120–180 minutes)
Mean estimated blood loss	665 cc (range, 150–1500 cc)
Rectal injury	None
Mean hospitalization	2.5 days (range, 2.0–6.0 days)
Continence	96% (mean time, 10 weeks)

Data from Clark et al.[8]

Australia, West Ryde, New South Wales) and estramustine (in an alternating sequential [KAVE] regimen) combined with androgen blockade. The results with respect to toxicity, nadir PSA before prostatectomy, local response, and surgical outcomes were similar to the results of the Cleveland Clinic Foundation trial described above. Furthermore, the pathologic results showed that the number of patients achieving pT0 (none in either of these trials), organ-confined disease (33% vs 31%), and extracapsular extension (67% vs 69%) in this trial compared with the Cleveland Clinic Foundation trial, respectively, were virtually identical; there was, however, a higher rate of invasion of the seminal vesicle and lymph node metastasis in the KAVE trial. The authors of this study, like the Cleveland Clinic Foundation study authors, concluded that radical prostatectomy after neoadjuvant chemohormonal therapy is feasible, but that KAVE combined with androgen blockade has minimal antitumor activity in patients with locally advanced disease.

Oh and colleagues[18] are currently conducting a trial of neoadjuvant docetaxel in a similar population of locally advanced patients at high-risk for failure. Docetaxel is being administered at 36 mg/m^2 weekly for up to 6 months, followed by radical prostatectomy. The patients are being monitored with monthly DRE, PSA measurements, and serial magnetic resonance imaging. In a preliminary report of 15 patients, therapy appears to be well tolerated, with only 1 patient developing clinical-disease progression.[18]

Docetaxel has demonstrated significant antitumor activity in patients with advanced, androgen-independent disease.

Conclusion

Our current ongoing study explores the antitumor response of a short course of single-agent docetaxel administered on a weekly schedule to patients with locally advanced prostate cancer. Docetaxel has demonstrated significant antitumor activity in patients with advanced, androgen-independent disease.[10] There is limited published information regarding the utility of chemotherapy (without hormonal therapy) in the neoadjuvant setting. In addition there is considerable uncertainty as to how best to assess the antitumor impact of this approach. Although evidence of tumor necrosis in the resected prostate would provide intriguing information, it is also conceivable that antitumor activity against micrometastatic disease may provide selected patients with a delay in time-to-tumor-recurrence. These and other critical questions will only be answered by randomized trials.

A virtual explosion of new "small molecules," both as single agents and in combination with traditional antineoplastics, has become available for clinical investigation. The ability to assess the activity of these new agents in prostate cancer may be potentially compromised by the widely recognized dilemma of assessing response in advanced prostate cancer.[19] A neoadjuvant evaluation of some

Main Points

- Studies have shown that patients with locally advanced prostate cancer—defined by preoperative characteristics of biopsy Gleason score, clinical T stage, and serum prostate specific antigen (PSA) levels—have worse outcomes after radical prostatectomy (RP) than patients with more favorable parameters.
- Results of these studies have led researchers to explore the use of chemotherapy as neoadjuvant treatment in patients with locally advanced disease.
- The current ongoing study of 28 patients has been investigating the use of docetaxel as a single agent in a neoadjuvant setting, based on its tolerability and demonstrated significant antitumor activity in patients with advanced, androgen-independent disease.
- This study examined the activity (PSA levels and antitumor response), feasibility, and tolerability of a regimen of single-agent docetaxel, 40 mg/m^2, administered intravenously on a weekly schedule for 6 weeks to patients with locally advanced prostate cancer before RP.
- The study results showed that 75% of the patients had reductions in prostate-specific antigen (PSA) levels ranging from 9%–79% at the completion of docetaxel therapy. PSA levels increased by 2%–18% in 25% of the patients, from baseline to completion of chemotherapy. All patients also maintained noncastrate levels of testosterone.
- The reporting of the primary endpoint of pathologic response is pending completion of accrual and surgery.

of these agents may provide a template with which to assess histologic response, along with other mechanistic, correlative studies, in a trial designed with relatively rapid turnover. ■

References

1. Whitmore WF. Proceedings: the natural history of prostatic cancer. *Cancer*. 1973; 32:1104–1112.
2. Catalona WJ, Smith DS. Cancer recurrence and survival rates after anatomic radical retropubic prostatectomy for prostate cancer: intermediate term results. *J Urol.* 1998;160(6 pt 2):2428–2434.
3. Pound CR, Partin AW, Epstein JI, Walsh PC. Prostate-specific antigen after anatomic radical retropubic prostatectomy: patterns of recurrence and cancer control. *Urol Clin North Am*. 1997;24:395–406.
4. Kupelian PA, Elshaikh M, Reddy CA, et al. Comparison of the efficacy of local therapies for localized prostate cancer in the prostate-specific antigen era: a large single-institution experience with radical prostatectomy and external-beam radiotherapy. *J Clin Oncol.* 2002;20:3376–3385.
5. Fair WR, Rabbani F, Bastar A, Betancourt J. Neoadjuvant hormone therapy before radical prostatectomy: update on the Memorial Sloan-Kettering Cancer Center Trials. *Mol Urol*. 1999;3:253–260.
6. Van Poppel H, DeRidder DD, Elgamal AA, et al. Neoadjuvant hormonal therapy before radical prostatectomy decreases the number of positive surgical margins in stage T2 prostate cancer: interim results of a prospective randomized trial. The Belgian Uro-Oncological Study Group. *J Urol*. 1995;154(2 pt 1):429–434.
7. Gleave ME, Goldenberg SL, Chin JL, et al. Randomized comparative study of 3 versus 8 month neoadjuvant hormonal therapy before radical prostatectomy: biochemical and pathological effects. *J Urol*. 2001;166:500–506.
8. Clark PE, Peereboom DM, Dreicer R, et al. Phase II trial of neoadjuvant estramustine and etoposide plus radical prostatectomy for locally advanced prostate cancer. *Urology*. 2001; 57:281–285.
9. Zelefsky MJ, Kelly WK, Scher HI, et al. Results of a phase II study using estramustine phosphate and vinblastine in combination with high-dose three-dimensional conformal radiotherapy for patients with locally advanced prostate cancer. *J Clin Oncol.* 2000;18:1936–1941.
10. Picus J, Schultz M. Docetaxel (Taxotere) as monotherapy in the treatment of hormone-refractory prostate cancer: preliminary results. *Semin Oncol.* 1999;26(5 suppl 17):14–18.
11. Van de Voorde WM, Elgamal AA, Van Poppel HP, et al. Morphologic and immunohistochemical changes in prostate cancer after preoperative hormonal therapy: a comparative study of radical prostatectomies. *Cancer*. 1994;74:3164–3175.
12. *AJCC Cancer Staging Handbook*. 4th ed. Philadelphia: Lippincott-Raven Publishers; 1992.
13. Klein EA, Kupelian PA, Tuason L, Levin HS. Initial dissection of the lateral fascia reduces the positive margin rate in radical prostatectomy. *Urology*. 1998;51:766–773.
14. Catalona WJ, Ramos CG, Carvalhal GF. Contemporary results of anatomic radical prostatectomy. *CA Cancer J Clin*. 1999;49:282–296.
15. Soloway MS, Sharifi R, Wajsman Z, et al. Randomized prospective study comparing radical prostatectomy alone versus radical prostatectomy preceded by androgen blockade in clinical stage B2 (T2bNxM0) prostate cancer. The Lupron Depot Neoadjuvant Prostate Cancer Study Group. *J Urol.* 1995;154(2 pt 1):424–428.
16. Goldenberg SL, Klotz LH, Srigley J, et al. Randomized, prospective, controlled study comparing radical prostatectomy alone and neoadjuvant androgen withdrawal in the treatment of localized prostate cancer. Canadian Urologic Oncology Group. *J Urol.* 1996;156:873–877.
17. Pettaway CA, Pisters LL, Troncoso P, et al. Neoadjuvant chemotherapy and hormonal therapy followed by radical prostatectomy: feasibility and preliminary results. *J Clin Oncol*. 2000;18:1050–1057.
18. Oh WK, George DJ, Kaufman DS, et al. Neoadjuvant docetaxel followed by radical prostatectomy in patients with high-risk localized prostate cancer: a preliminary report. *Semin Oncol.* 2001;28(4 suppl 15):40–44.
19. Dreicer R. Metastatic prostate cancer: assessment of response to systemic therapy. *Semin Urol Oncol.* 1997;15:28–32.